ORIGINAL RESEARCH

Effectiveness and Safety of Dabigatran and Warfarin in Real-World US Patients With Non-Valvular Atrial Fibrillation: A Retrospective Cohort Study

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***Background*—**The recent availability of dabigatran, a novel oral anticoagulant, provided a new treatment option for stroke prevention in atrial fibrillation beyond warfarin, the main therapy for years. Little is known about their real-world comparative effectiveness and safety, even less among patient demographic and clinical subgroups.

***Methods and Results*—**Using a cohort of non-valvular AF patients initiating anticoagulation from October 2010 to December 2012 drawn from a large US database of commercial and Medicare supplement claims, we applied propensity score weights to Cox proportional hazards regression to assess the comparative effectiveness and safety of dabigatran versus warfarin. Analyses were repeated among clinical and demographic subgroups using stratum-specific propensity scores as an exploratory analysis. Of the 64 935 patients initiating anticoagulation, 32.5% used dabigatran. Compared with warfarin, dabigatran was associated with a lower risk of ischemic stroke or systemic embolism (composite adjusted Hazard Ratio [aHR], 95% CI: 0.86, 95% CI: 0.79 to 0.93), hemorrhagic stroke (aHR: 0.51, 0.40 to 0.65), and acute myocardial infarction (aHR: 0.88, 95% CI: 0.77 to 0.99), and no relation was seen between dabigatran and the composite harm outcome (aHR: 0.94, 95% CI: 0.87 to 1.01). However, dabigatran was associated with a higher risk of gastrointestinal bleeding (aHR: 1.11, 95% CI: 1.02 to 1.22). Estimates of effectiveness and safety appeared to be mostly similar across subgroups.

***Conclusions*—**Dabigatran could be a safe and potentially more effective alternative to warfarin in patients with atrial fibrillation managed in routine practice settings. **(*J Am Heart Assoc*. 2015;4:e001798 doi: 10.1161/JAHA.115.001798)**

Key Words: anticoagulants • atrial fibrillation • dabigatran • novel oral anticoagulants • warfarin

Using anticoagulation in patients with atrial fibrillation (AF) is recommended to prevent stroke and systemic embolism.[1] Warfarin has been the only oral anticoagulant available for the past few decades; however, warfarin has a narrow therapeutic index that requires monitoring and has a number of notable drug-drug and drug-food interactions.[1] Recent availability of dabigatran, one of the novel oral anticoagulants (NOACs), has provided an additional option with some practical advantages including no currently recommended routine blood monitoring requirements and fewer interactions; however, dabigatran also lacks a convenient agent to reverse bleeding.[2,3]

Despite similar or superior efficacy in the Randomized Evaluation of Long Term Therapy (RE-LY) With Dabigatran Etexilate trial used for Food and Drug Administration (FDA) approval, the comparative effectiveness and safety of dabigatran compared with warfarin is still unclear, particularly in commercially insured individuals younger than 65 years of age in real-world clinical practice.[4] Even less is known about the comparative clinical outcomes among important clinical and demographic subgroups, particularly among subgroups that may have been partly excluded in RE-LY, such as patients with major renal insufficiency and recent, previous stroke. In addition, the rates of adverse events submitted to the FDA have also been higher for dabigatran compared with warfarin since dabigatran's market availability, but the FDA

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has since found no increased risk of adverse outcomes in a large analysis of Medicare patients treated in clinical practice.[5,6]

Therefore, we compared the effectiveness and safety of dabigatran with warfarin in clinical practice among a large nationally representative retrospective cohort of commercially insured patients in the United States after availability of the new oral anticoagulants, while also examining within subgroups of patients with different underlying characteristics. We sought to (1) assess the risk of ischemic stroke, systemic embolism, acute myocardial infarction, or clinically significant bleeding events among AF patients using dabigatran compared with warfarin, and (2) explore the risk of these same outcomes among strata of patients with clinically relevant characteristics that may influence comparative effectiveness.

Methods

Setting and Participants

We conducted a retrospective cohort study using the Truven Health MarketScan Commercial Claims and Encounters and Medicare supplement databases for the years 2009–2012. These data files comprise patient-specific medical inpatient and outpatient claims, physician office visits, outpatient pharmaceutical data, and enrollment data for approximately 40 million individuals from over 100 nationwide employer-provided plans annually. Prescription medication use was identified through National Drug Codes (NDCs) in the outpatient prescription files, including use of anticoagulation therapies.

A cohort of patients with AF was selected from the following inclusion criteria: (1) filling ≥1 prescription for warfarin or dabigatran after 10/19/2010 (dabigatran FDA approval date), hereafter referred to as the "index prescription"; (2) ≥18 years of age at index prescription fill date; (3) receiving at least 1 inpatient or 2 outpatient International Classification of Diseases, ninth edition (ICD-9) codes for AF (ICD-9: 427.31) occurring on separate days within 12 months before the index fill date; and (4) were continuously enrolled for at least 12 months prior to the index fill date. One of the outpatient ICD-9 AF codes could occur after the index prescription fill date, but the 2 ICD-9 codes must have occurred on separate days to eliminate the possibility of the code being used as a rule-out condition. In addition, patients were excluded from the study if they had an anticoagulant prescription fill in the 12 months prior to the index prescription fill to examine new users of anticoagulation. Moreover, patients with ICD-9 codes related to valvular or transient AF in the baseline period were excluded (Table 1).

Outcome Measurements

Clinically important outcomes were measured in the follow-up period after anticoagulant initiation. Clinical effectiveness was defined as a composite of the occurrence of ischemic stroke, TIA, and other thromboembolic events in the follow-up period. Harm was defined as a composite of intracranial hemorrhage or hemorrhagic stroke, gastrointestinal (GI) hemorrhage, or other bleeding. Acute myocardial infarction was also assessed as an outcome, but was not included in either of the clinical effectiveness or harm composite outcomes. Outcomes were assessed based on the presence of inpatient claims with either a primary or secondary diagnosis. Validated ICD-9 coding algorithms were used to measure the outcome events, which are based on published studies found in the literature (Table 1).[7–11] Patients were followed from the time of anticoagulant initiation and continued until loss of continuous eligibility, occurrence of a study outcome of interest, or end of the administrative period (December 31, 2012).

Baseline Characteristics/Covariates

Patient demographic characteristics were identified in the 12-month baseline based on their noted associations with anticoagulant use and the clinical outcomes. Specific demographics included: age, census region of residence (northeast, north central, south, west), type of health benefit plan (comprehensive, health maintenance organization, point-of-service, preferred provider organization, consumer-driven health plan), gender, and a measure of the generosity of the prescription drug benefit.[12] Specifically, patients' cost-sharing proportions for all prescriptions in the 12 months prior to anticoagulant initiation were divided by the total net drug payments as a benefits' generosity measure.[12] This proportion was categorized into 3 ratio levels that were paid by patients: >0.80 ("No/Poor coverage"), 0.20 to 0.80 ("Fair coverage), and ≤0.20 ("Good coverage").

Patient comorbidities were also identified in the 12-month baseline period using ICD-9 codes in the outpatient and inpatient medical claims files based on previous literature.[13–15] These comorbidities included previous ischemic stroke, venous thromboembolism (VTE), congestive heart failure (CHF), hypertension, hyperlipidemia, acute myocardial infarction (AMI), coronary artery disease, bleeding, anemia, peripheral vascular disease, renal impairment, anemia, diabetes mellitus, peptic ulcer disease, dementia, and sleep apnea. Clinical prediction risk scores, such as CHA_2DS_2-VASc score (ischemic stroke risk), ATRIA score (bleeding risk), and the Charlson Comorbidity index score, were also measured.[13–15] Briefly, the CHA_2DS_2-VASc score incorporates congestive heart failure, hypertension, age 65 to 74, age ≥75 years, diabetes, prior ischemic stroke, female gender, coronary artery disease and peripheral vascular disease and was

Table 1. Coding Schematics for Exclusion Criteria and Outcome Definitions

Outcome	ICD-9 Codes	Diagnosis Position
Exclusion criteria		
Liver disease	571.1, 571.3, 571.5, 571.8, 571.9, 572.8, 573.3, 573.9	Any
Coagulation deficiency	269.0, 286.0 to 286.8, 286.52, 286.53, 286.59	Any
Mitral valve replacement	35, 37, 35.1, 35.2, 35.9, 35.12, 35.23, 35.24, 35.9, 35.96, 35.97, 37.4, 37.35, 37.4, 37.41	Any
Heart valve replacement	V42.2, V43.3	Any
Mitral stenosis	394.0, 394.2, 396.0, 396.1, 396.8	Any
Atrial flutter	427.32	Any
Hyperthyroidism	242, 242.0, 242.1, 242.2, 242.3, 242.9	Any
Clinical effectiveness outcomes		
Ischemic stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434 (excluding 434.x0), 436	Primary or secondary
Transient ischemic attack	435	Primary
Venous thromboembolism (DVT, PE)	415, 451, 453	Primary or secondary
Safety outcomes		
Hemorrhagic stroke/intracranial hemorrhage	430, 431, 432	Primary or secondary
Gastrointestinal hemorrhage	455.2, 455.5, 455.8, 456.0, 456.20, 459.0, 530.82, 578	Any
Other bleeding events	423.0, 593.81, 599.7, 719.11, 784.7, 784.8, 786.3	Any
Acute myocardial infarction	410.x1	Primary or secondary

DVT indicates deep vein thrombosis; PE, pulmonary embolism.

categorized into the following 3 levels: 0 (low risk), 1 (intermediate risk), and ≥2 (high risk). The ATRIA score includes anemia, severe renal disease, age ≥75 years, previous hemorrhage and hypertension and was categorized as follows: ≤3 (low risk), 4 (intermediate risk), and ≥5 (high risk), conforming to previous standards. Of the bleeding clinical prediction risk scores, the ATRIA score is considered to be more reliably measured in secondary medical claims compared with other bleeding risk indices.[15–17] Concomitant medication therapies were also measured because of known associations with anticoagulation, including antiplatelet therapies, gastroprotective agents, antiarrhythmics, rate control therapies (eg, digoxin, beta-blockers, calcium channel blockers), and statins.

Statistical Analysis

Descriptive statistics were generated including the outcome rates per 1000 person years in each anticoagulant group and distributions of baseline characteristics. The absolute standardized difference was also used to compare the baseline characteristics between warfarin and dabigatran users, whereby significant imbalance of baseline characteristics between groups is usually characterized by an absolute standardized difference >10.[18]

We estimated adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs) using Cox proportional hazards regression models with stabilized inverse probability treatment weighting (IPTW).[19] These propensity score weights were estimated using logistic regression that included all variables in Table 2 as covariates. The propensity score distributions were examined by exposure status for overlap to assess factors associated with overall treatment selection and comparability of the covariate distributions. We then estimated the treatment effects using propensity score weighting, including IPTW approaches, trimming for non-overlapping regions.[19] The estimated weights were incorporated into the Cox regression models that only included the anticoagulant treatment variable. Various sensitivity analyses were conducted in which we varied the outcome definitions and how the propensity score was used. These were repeated analyses that included outcomes occurring in the outpatient setting, examining patients who lost continuous eligibility, stratifying by type of beneficiary (commercially insured or Medicare supplement), and restricting to patients with newly diagnosed AF. We also examined the proportion of patients with in-hospital death that was observed in the patients' hospital discharge statuses.

We repeated these analyses among subgroups of patients with demographic and clinical characteristics that may

Table 2. Baseline Characteristics of Patients With AF Initiating Anticoagulation, 2010–2012

Baseline Characteristic	Warfarin, N (%)	Dabigatran, N (%)	Absolute SD
Demographic			
Age, y			
<55	3886 (8.9)	2963 (14.1)	20.2
55 to 64	10 146 (23.1)	6443 (30.6)	20.5
65 to 74	9792 (22.3)	4838 (23.0)	2.1
≥75	20 041 (45.7)	6826 (32.4)	34.3
Mean (standard deviation)	71.4 (12.2)	67.5 (12.4)	
Male gender	25 562 (58.3)	13 363 (63.4)	11.6
Region			
Northeast	7589 (17.3)	3513 (16.7)	2.1
North central	15 408 (35.1)	6107 (29.0)	15.7
South	12 181 (27.8)	7864 (37.3)	26.1
West	7732 (17.6)	3259 (15.5)	7.2
Insurance plan			
Comprehensive	15 701 (35.8)	6812 (32.3)	8.9
HMO	6368 (14.5)	1723 (8.2)	24.3
POS	1973 (4.5)	1226 (5.8)	8.6
PPO	16 889 (38.5)	9766 (46.4)	19.4
CDHP	707 (1.6)	464 (2.2)	6.7
Good benefits' generosity (≤0.20)	19 595 (44.7)	10 611 (50.4)	13.5
Clinical			
Ischemic stroke	4710 (10.7)	1495 (7.1)	18.9
Congestive heart failure	12 414 (28.3)	3851 (18.3)	32.7
Venous thromboembolism	5385 (12.3)	538 (2.6)	81.8
Hyperlipidemia	21 710 (49.5)	10 456 (49.6)	0.2
Hypertension	32 043 (73.0)	14 578 (69.2)	9.1
Myocardial infarction	2001 (4.6)	500 (2.4)	19.9
Coronary artery disease	15 000 (34.2)	5942 (28.2)	16.5
Peripheral vascular disease	3892 (8.9)	1150 (5.5)	20.2
Renal impairment	5517 (12.6)	1210 (5.7)	39.8
Diabetes	13 957 (31.8)	5610 (26.6)	14.6
Bleeding	5975 (13.6)	1983 (9.4)	19.1
Anemia	8736 (19.9)	2241 (10.6)	39.4
Peptic ulcer disease	320 (0.7)	93 (0.4)	6.7
Sleep apnea	4546 (10.4)	2526 (12.0)	6.6
Cognitive deficiency	438 (1.0)	126 (0.6)	7.3
Hospitalizations (≥1)	4710 (10.7)	1495 (7.1)	18.9
Catheter ablation	12 414 (28.3)	3851 (18.3)	32.7
CCI			
0	10 051 (22.9)	7091 (33.7)	28.7
1 to 2	17 657 (40.3)	9058 (43.0)	6.5

Continued

Table 2. Continued

Baseline Characteristic	Warfarin, N (%)	Dabigatran, N (%)	Absolute SD
3 to 5	11 871 (27.1)	4001 (19.0)	26.2
6 to 8	3165 (7.2)	686 (3.3)	29.9
≥9	1121 (2.6)	234 (1.1)	20.1
CHA_2DS_2-VASc score			
0	2182 (5.0)	1881 (8.9)	24.3
1	5121 (11.7)	3981 (18.9)	29.2
≥2	36 562 (83.4)	15 208 (72.2)	28.6
Mean (standard deviation)	2.9 (1.7)	2.3 (1.6)	
ATRIA score			
0 to 3	30 667 (69.9)	17 602 (83.5)	65.8
4	4158 (9.5)	1501 (7.1)	12.6
≥5	9040 (20.6)	1967 (9.3)	50.6
Mean (standard deviation)	2.9 (2.4)	2.0 (1.9)	
Medication use			
Antiplatelet therapy*	5726 (13.1)	2684 (12.7)	1.6
Gastroprotective agent	5558 (12.7)	2267 (10.8)	8.2
Antiarrhythmic	9991 (22.8)	5344 (25.4)	7.6
Digoxin	7435 (16.9)	2973 (14.1)	10.5
Beta-blocker	29 513 (67.3)	14 132 (67.1)	0.5
Calcium channel blocker	18 501 (42.2)	8602 (40.8)	3.4
ACEI/ARB	25 001 (57.0)	11 891 (56.4)	1.4
Statin	23 964 (54.6)	11 205 (53.2)	3.2
Hormone	1626 (3.7)	959 (4.6)	6.0

ACEI indicates angiotensin-converting-enzyme inhibitor; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CCI, Charlson Comorbidity Index; CDHP, consumer-driven health plan; HMO, health maintenance organization; POS, Point-of-service; PPO, preferred provider organization; SD, standardized difference.
*Antiplatelet therapy measurement did not include aspirin due to data availability.

influence treatment selection and effects as exploratory analyses. The propensity score was re-estimated within each subgroup in the regression models. These demographic subgroups were gender groups, age groups, and patients with different prescription benefits' generosity levels, and the clinical subgroups included patients with previous ischemic stroke, VTE, CHF, AMI, renal insufficiency, and diabetes. Lastly, strata of patients with different ATRIA and CHA_2DS_2-VASc scores were also examined.

Statistical significance was determined using 2-sided tests with alpha=0.05. All analyses were conducted using SAS 9.3 (Cary, NC). The University of North Carolina at Chapel Hill Institutional Review Board reviewed this study, and it received exempt approval status.

Results

In total, 64 935 AF patients met study criteria, with 21 070 (32.5%) using dabigatran and 43 865 (67.5%) using warfarin (Figure 1). The mean age of the cohort was 69.9 years (standard deviation [SD] 12.4), and 42 334 (60.1%) were male. Measured baseline demographic and clinical characteristics of the AF patients are provided in Table 2. New users of dabigatran were more likely to be younger, male, from the South region, use high-deductible health or preferred provider organization insurance health plans, and have good prescription benefits coverage (ratio ≥0 and ≤0.20) for medications filled within the previous 12 months. Patients using warfarin for the first time were more likely to have experienced relevant comorbidities, particularly ischemic stroke, CHF, and VTE.

The estimated densities of the propensity scores are shown in Figure 2A. After examining the individual covariates, the ones most contributing to the slight non-overlap seen in the warfarin group were the baseline prescription benefits' generosity and venous thromboembolism covariates, despite their association with both exposure and outcomes (Figure 2B). These characteristics were examined further in stratum-specific estimates and sensitivity analyses. However,

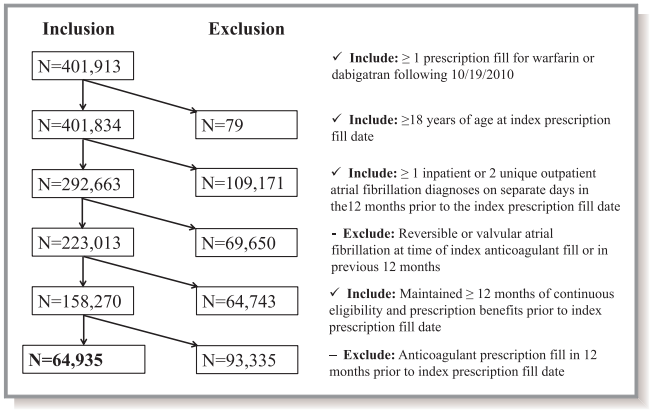


Figure 1. Cohort schematic of new dabigatran or warfarin users in patients with atrial fibrillation.

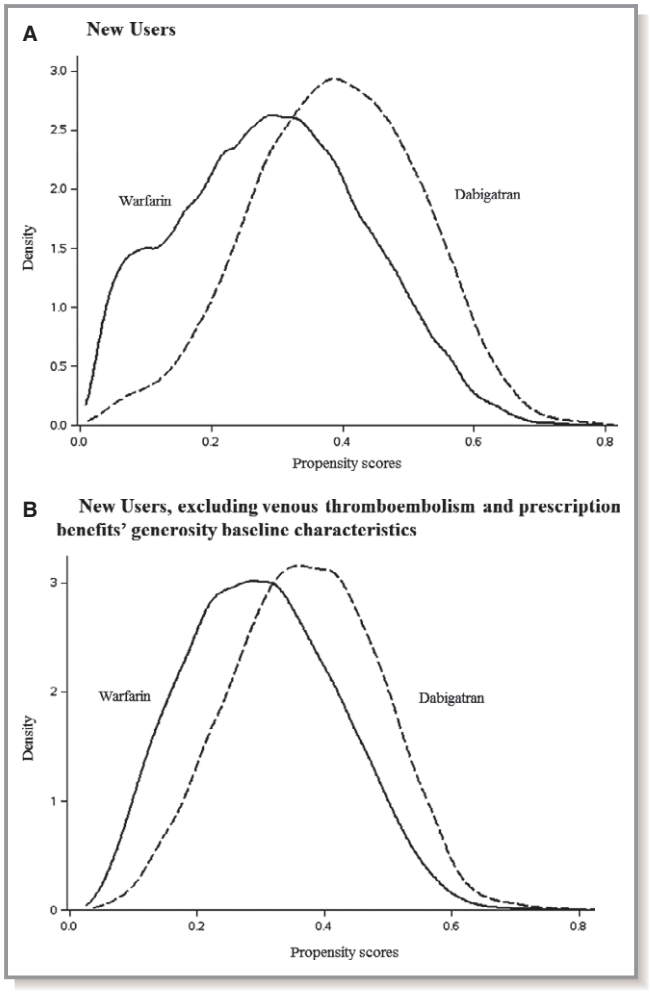


Figure 2. Estimated propensity score kernel densities among new users of dabigatran and warfarin.

the c-statistic for the main propensity score was 0.69, indicating a good fit, and there was a high degree of overlap. There was also no imbalance in covariates after propensity score weighting (Table 3).

The mean patient follow-up time from initiation was 358 days (SD 224 days). Table 4 shows the comparative effectiveness and harm outcomes among all anticoagulant initiators, including unadjusted outcome rates. In the warfarin group, there were 48.6 effectiveness composite events per 1000 person years compared with 30.2 events per 1000 person years in the dabigatran group. The outcome rate for the harm composite was 51.6 events per 1000 person years and 31.8 events per 1000 person years in the warfarin and dabigatran groups, respectively.

The PS-adjusted HR of the effectiveness composite for dabigatran users compared with warfarin was 0.86 (95% CI: 0.79 to 0.93). For the harm composite, the aHR for users of dabigatran compared with warfarin was (aHR: 0.94, 95% CI: 0.87 to 1.01). Using dabigatran compared with warfarin was associated with a 12% reduction in the hazard of experiencing AMI (aHR: 0.88, 95% CI: 0.77 to 0.99). Initiating dabigatran also resulted in a statistically significant reduction in the hazard of VTE (aHR: 0.70, 95% CI 0.60 to 0.80), hemorrhagic stroke (aHR: 0.51, 95% CI: 0.40 to 0.65), and other bleeding (aHR: 0.76, 96% CI: 0.65 to 0.89) compared with warfarin initiation. However, dabigatran was also associated with an increased hazard of GI hemorrhage (aHR: 1.11, 95% CI: 1.02 to 1.22). The PS-adjusted survival curves between dabigatran and warfarin users for experiencing the effectiveness composite, harm composite, and AMI are shown in Figure 3. Other sensitivity analyses are shown in Table 5 and yielded similar associations with slightly differing magnitudes, but the overall conclusions were robust to these modifications. Of the 14 219 warfarin patients hospitalized in the follow-up period after initiation, 381 (2.7%) were coded as "Died" or "Other died status" upon discharge; by contrast, of the 5932 dabigatran patients hospitalized in the follow-up, 95 (1.6%) were similarly coded.

Table 6 shows the estimated comparative effectiveness and safety among the examined subgroups after propensity score adjustment using stratum-specific weighting and forest plots of the aHRs and 95% CIs. The estimates of effectiveness compared with the original HR appeared to be similar across subgroups; the magnitudes appeared to be slightly stronger in some subgroups. Compared with the original HR, most of the adjusted HRs showed no relation between dabigatran use and an increased or decreased risk of harm outcomes. Compared with warfarin users, male patients, patients <55 years of age or 55 to 64 years of age, and patients with low or intermediate bleeding risk appeared to possibly have a decreased risk of a harm outcome using dabigatran. Lastly, compared with the original HR, the slight protective association against the risk of AMI using dabigatran compared with warfarin persisted in many subgroups; however, due to wide 95% CIs resulting from a small number of outcomes, no significant relation was also seen in some groups.

Table 3. Balance of Covariates After Applying the IPTW Propensity Scores Among Users of Dabigatran and Warfarin

Baseline Characteristic	Warfarin, %	Dabigatran, %	Absolute SD
Demographic			
Age, y			
<55	10.5%	10.2%	1.3
55 to 64	25.6%	25.3%	0.9
65 to 74	22.5%	22.8%	0.9
≥75	41.4%	41.8%	1.0
Male gender	59.9%	59.2%	1.6
Region			
Northeast	16.7%	17.3%	2.1
North Central	33.1%	33.0%	0.3
South	31.0%	31.1%	0.3
West	16.9%	17.2%	1.0
Insurance plan			
Comprehensive	34.4%	35.6%	2.4
HMO	12.4%	11.8%	0.6
POS	4.9%	4.8%	1.5
PPO	41.1%	41.7%	1.2
CDHP	1.8%	1.8%	0.0
Good benefits' generosity (≤0.20)	46.5%	46.0%	1.2
Clinical			
Ischemic stroke	9.6%	10.1%	2.3
Congestive heart failure	25.1%	26.4%	3.8
VTE	9.1%	10.5%	6.6
Hyperlipidemia	49.6%	50.1%	1.2
Hypertension	71.9%	72.5%	1.2
Myocardial infarction	3.9%	3.9%	0.0
Coronary artery disease	32.3%	33.1%	2.1
Peripheral vascular disease	7.8%	8.6%	4.0
Renal impairment	10.4%	11.2%	3.5
Diabetes	30.1%	30.7%	1.6
Bleeding	12.3%	13.0%	2.8
Anemia	16.9%	17.7%	2.8
Peptic ulcer disease	0.6%	0.7%	1.8
Sleep apnea	11.0%	11.5%	2.1
Cognitive deficiency	0.9%	1.0%	1.5
≥1 hospitalizations	53.4%	53.7%	0.7
Catheter ablation	1.3%	1.3%	0.0
CCI			
0	26.3%	25.6%	2.0
1 to 2	41.2%	40.3%	2.2
3 to 5	24.5%	25.2%	2.1

Continued

Table 3. Continued

Baseline Characteristic	Warfarin, %	Dabigatran, %	Absolute SD
6 to 8	5.9%	6.6%	4.1
≥9	2.1%	2.3%	2.0
CHA_2DS_2-VASc score			
0	6.2%	6.0%	1.1
1	14.0%	13.7%	1.1
≥2	79.7%	80.3%	1.6
ATRIA score			
0 to 3	74.3%	73.2%	2.7
4	8.7%	8.9%	1.0
≥5	17.0%	17.9%	3.1
Medication use			
Antiplatelet therapy*	13.0%	13.4%	0.7
Gastroprotective agent	12.0%	11.8%	0.8
Antiarrhythmic	23.7%	23.9%	0.6
Digoxin	16.1%	16.8%	2.5
Beta-blocker	67.2%	67.9%	1.6
Calcium channel blocker	41.8%	42.5%	1.7
ACEI/ARB	56.9%	57.5%	1.4
Statin	54.2%	54.7%	1.1

ACEI indicates angiotensin-converting-enzyme inhibitor; ARB, angiotensin receptor blocker; CCI, Charlson Comorbidity Index; CDHP, consumer-driven health plan; HMO, health maintenance organization; IPTW, inverse probability treatment weighting; POS, point-of-service; PPO, preferred provider organization; SD, standardized difference; VTE, venous thromboembolism.
*Antiplatelet therapy measurement did not include aspirin due to data availability.

Discussion

In this large cohort study of 64 935 AF patients, we examined the comparative effectiveness and safety of patients initiating warfarin or dabigatran for stroke prevention. We found a consistent decreased risk of systemic embolism, ischemic stroke, and AMI in patients using dabigatran compared with warfarin and did not find evidence of an increased risk of

Table 4. Estimated Treatment Effects in Patients With AF Using Dabigatran Compared With Warfarin

Outcome Type	Warfarin Events/1000 Person-Years	Dabigatran Events/1000 Person-Years	Unadjusted HR (95% CI)	Adjusted (PS-IPTW) HR (95% CI)
Effectiveness				
Composite	48.6	30.2	0.62 (0.57 to 0.68)**	0.86 (0.79 to 0.93)**
Ischemic stroke	35.6	17.3	0.74 (0.70 to 0.79)**	0.91 (0.81 to 1.02)
TIA	11.3	9.2	0.83 (0.70 to 0.97)*	1.07 (0.91 to 1.25)
VTE	20.4	9.1	0.45 (0.38 to 0.52)**	0.70 (0.60 to 0.80)**
Safety				
Composite	51.6	31.8	0.61 (0.56 to 0.67)**	0.94 (0.87 to 1.01)
Hemorrhagic stroke	8.0	3.3	0.41 (0.31 to 0.53)**	0.51 (0.40 to 0.65)**
GI hemorrhage	32.1	21.8	0.68 (0.61 to 0.75)**	1.11 (1.02 to 1.22)*
Other bleeding	14.4	8.1	0.56 (0.48 to 0.67)**	0.76 (0.65 to 0.89)**
AMI	19.1	13.1	0.66 (0.57-.0.76)**	0.88 (0.77 to 0.99)*

AF indicates atrial fibrillation; AMI, acute myocardial infarction; GI, gastrointestinal; HR, hazard ratio; IPTW, inverse probability treatment weighting; PS, Propensity score; TIA, transient ischemic attack; VTE, venous thromboembolism.
*P<0.05; **P<0.001.

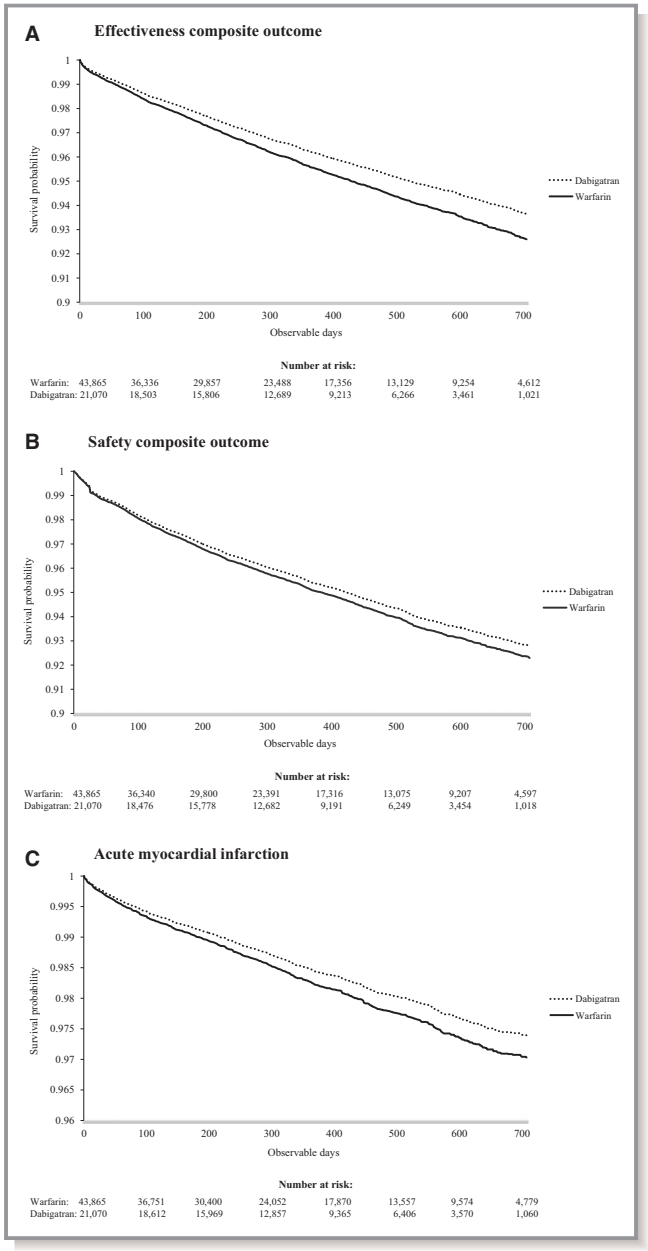


Figure 3. Adjusted survival curves of dabigatran and warfarin users and the risk of an effectiveness composite outcome, a safety composite outcome, and acute myocardial infarction.

harm outcomes with the exception of GI hemorrhage. In the exploratory analyses, with a few exceptions, dabigatran did not appear to increase the risk of outcomes across the subgroups. AMI risk also did not appear to differ drastically among subgroups, largely due to wide 95% CIs resulting from a small number of outcomes. However, these subgroup analyses should be interpreted with much caution as they were exploratory and intended for hypothesis generation in future research.

Until recently, previous studies examining the comparative effectiveness and safety of dabigatran versus warfarin have mainly drawn from the RE-LY study used for FDA approval and meta-analyses including the other studied NOACs.[3,20,21] The meta-analyses broadly found dabigatran to have similar or better efficacy in preventing ischemic stroke and systemic embolism compared with warfarin but significantly better safety, particularly in reducing intracranial bleeding and hemorrhagic stroke.[3,4,22] In a large study of Medicare patients, Graham et al found that dabigatran was associated with a lower risk of ischemic stroke, intracranial hemorrhage and death, and increased risk of major GI hemorrhage compared with warfarin. Hernandez et al found that dabigatran was associated with a higher risk of major bleeding and GI bleeding with a lower risk of intracranial hemorrhage in a smaller subset of Medicare patients. A few other studies in real-world clinical practice have either been conducted in Europe or included small sample sizes, and these have shown similar results as our study.[23–25] A recent report by the FDA of a very large cohort of Medicare patients with atrial fibrillation found similar associations with lower risk of clot-related strokes, intracranial bleeding, and death compared with warfarin.[26] Overall, some controversy surrounding the relative bleeding rates between dabigatran and warfarin still exists and more research is warranted.

The results of our study are consistent with most previous results in that we have found that dabigatran appears to be more effective than warfarin in preventing ischemic stroke and systemic embolism. Unlike the RE-LY trial, where patients were subject to regular follow-up dictated by a study protocol, in our study, these were patients in real-world practice. Indeed, our study's absolute event rates for ischemic stroke or systemic embolism were approximately twice the event rates in the RE-LY study. However, this is expected, as we included a wider population of patients managed in real-world practice with non-valvular AF, as reflected by the relatively higher mean ischemic stroke risk scores. Just as in the RE-LY trial, GI bleeding was also higher among dabigatran patients compared with warfarin patients in our study, but overall, there were otherwise no general differences in the risk of harm or adverse outcomes. Compared with the recent studies in the Medicare population by Graham et al and Hernandez et al, while we examined commercially insured patients, we found similar increased risks of GI hemorrhage as in both of these studies and lower risk of ischemic stroke as in the study by Graham et al.[6,27] Our study found no difference in the risks of major bleeding between the 2 groups, but a lower risk of hemorrhagic stroke, which was slightly different than these 2 studies. In these studies, Graham et al found a decreased risk of all types of bleeding except for GI, and Hernandez et al found an increased risk in all but intracranial hemorrhage.[6,27] In addition to population differences, there were also some differences in study design.

Table 5. Sensitivity Analyses of Estimated Treatment Effects in AF Patients Using Dabigatran Compared With Warfarin

Outcome Type	Effectiveness Composite PS-IPTW HR (95% CI)	Safety Composite PS-IPTW HR (95% CI)	AMI Outcome PS-IPTW HR (95% CI)
Original results	0.86 (0.79 to 0.93)**	0.94 (0.87 to 1.01)	0.88 (0.77 to 0.99)*
1. Exclude VTE and prescription benefits' generosity from PS	0.81 (0.74 to 0.88)**	0.81 (0.75 to 0.88)**	0.90 (0.79 to 1.03)
2. Restrict to newly-diagnosed AF	0.83 (0.74 to 0.94)*	0.79 (0.71 to 0.89)**	0.85 (0.71 to 1.01)
3. Restrict to commercially-insured patients	0.70 (0.59 to 0.83)**	0.74 (0.63 to 0.88)**	0.76 (0.58 to 0.99)*
4. Restrict to medicare supplemental patients	0.88 (0.79 to 0.97)	0.85 (0.77 to 0.94)*	0.88 (0.75 to 1.03)
5. Include outpatient ICD-9 codes (same diagnosis positions)	0.70 (0.67 to 0.74)**	1.02 (0.99 to 1.05)	N/A
6. Include patients who lost continuous eligibility in outcome definition	0.92 (0.89 to 0.96)**	0.97 (0.94 to 0.99)**	0.90 (0.79 to 1.03)

AF indicates atrial fibrillation; HR, hazard ratio; PS, propensity score; IPTW, inverse probability treatment weighting; AMI, acute myocardial infarction; VTE, venous thromboembolism; TIA, transient ischemic attack; ICD, international classification of disease.
*$P<0.05$; **$P<0.001$.

Our study also explored the effects of anticoagulation among patient subgroups. Among the pre-specified clinically relevant demographic and clinical subgroups, the effects were similar to those observed in the full cohort, although there was some possible variation among the sub-groups. Moreover, we noted with some potential concern that our estimates trended towards a possible increased risk of adverse outcomes among women using dabigatran compared with warfarin. Previous research has indicated that women may benefit from more aggressive anticoagulation than men, and our results could reflect these conclusions.[28] The fact that dabigatran did not appear to increase the risk of experiencing one of the composite outcomes in almost all of the sensitivity analyses and subgroup analyses may be reassuring. Perhaps some residual unmeasured confounding could provide an explanation for any differences noted. Further research is warranted to continue to explore potential areas of heterogeneity in treatment effects among patient subgroups, and we strongly caution against overinterpretation of the estimates as these exploratory analyses were intended to be used for hypothesis generation only.

Our study has several limitations. First, this is an observational study, and despite adjusting for a wide range of comorbidities, some residual confounding is likely because of unmeasured or inadequately measured confounders.[29–31] Because patients at higher risk of stroke or bleeding were more likely to use warfarin, covariate adjustment moved the estimate closer to the null than the unadjusted estimate, and unmeasured confounding could overestimate the benefit and underestimate the harms from dabigatran.[32] Renal insufficiency was measured using claims, because creatinine clearance was not available in the database. AF duration was also unavailable. Refill records from commercial claims databases may also not fully reflect medication use. Patients may not take medications as filled and also may fill prescriptions outside of their pharmacy benefit; thus, some of the new users may be continuing users, and some may not be taking their medication.[33,34] However, refill records are generally a widely accepted means of assessing medication exposure and have been shown to have good validity, correlation, and similar sensitivity and specificity with other measurements, including self-report, pill counts, and electronic records.[35,36]

In addition, information about mortality is also not available in the database, which may have biased the survival analysis. This limitation was explored by including patients who lost continuous eligibility in the outcome definition (which could possibly have been a consequence of dying), and while the estimates moved much closer to the null, the overall direction of the estimates remained similar. In-hospital deaths were also examined, and there was a higher proportion in the warfarin group. We also could not account for site-level variance due to data limitations. Lastly, because over-the-counter medication use was not available in the database, we could not measure concomitant aspirin use.

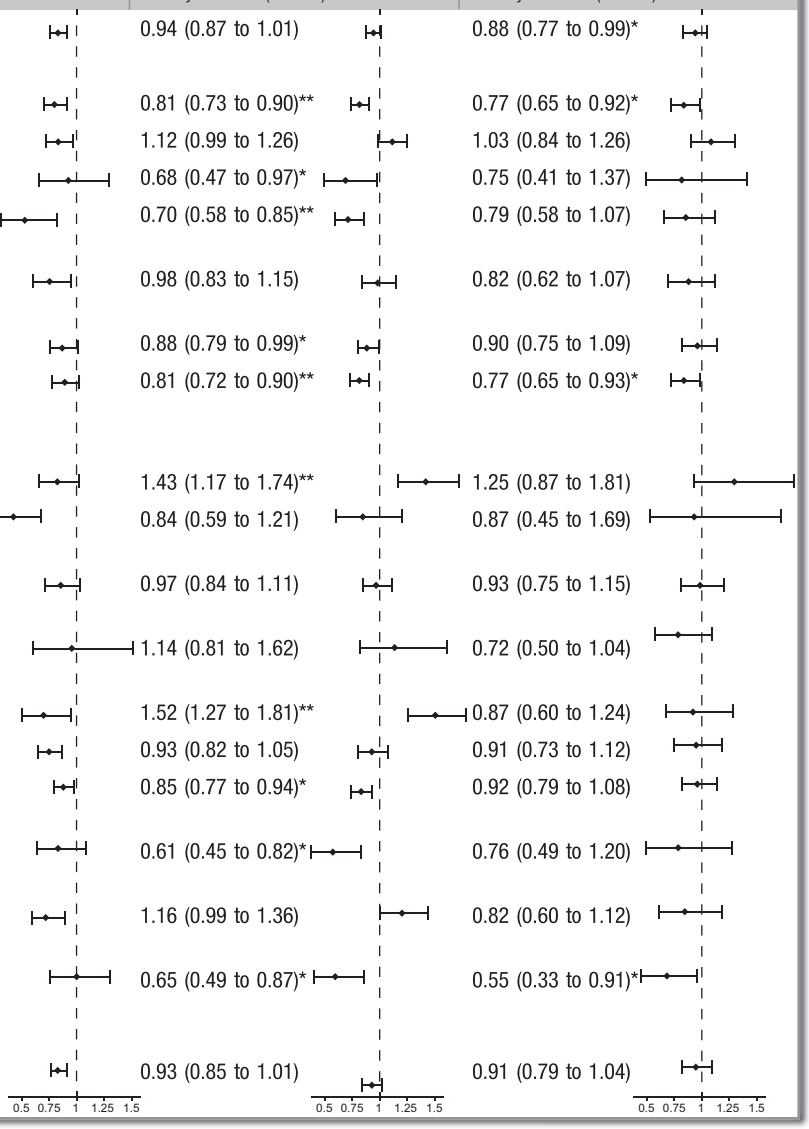
There are several strengths of this study. This research used a large database of nationally representative commercially insured patients, including some Medicare beneficiaries. Moreover, most previous research outside the original clinical trials to our knowledge examining the use of the novel anticoagulants, particularly in younger patients, has been conducted in Europe or in smaller databases. This study also examined effectiveness and safety >2 years after dabigatran became available and among patient demographic and clinical subgroups.

Conclusion

Our retrospective cohort study suggests that dabigatran could be equally safe and possibly more effective than warfarin in commercially insured patients in clinical practice.

Table 6. Estimated Treatment Effects in Strata of AF Patients With Certain Baseline Demographic and Clinical Characteristics Using Dabigatran Compared With Warfarin

Patient Subgroups	Effectiveness Composite PS-Adjusted HR (95% CI)	Safety Composite PS-Adjusted HR (95% CI)	AMI Outcome PS-Adjusted HR (95% CI)
Full cohort (N=64 985)	0.86 (0.79 to 0.93)**	0.94 (0.87 to 1.01)	0.88 (0.77 to 0.99)*
Demographic subgroups			
Male gender (N=38 925)	0.83 (0.74 to 0.93)**	0.81 (0.73 to 0.90)**	0.77 (0.65 to 0.92)*
Female gender (N=26 010)	0.86 (0.76 to 0.98)*	1.12 (0.99 to 1.26)	1.03 (0.84 to 1.26)
Age <55 years (N=6849)	0.94 (0.70 to 1.26)	0.68 (0.47 to 0.97)*	0.75 (0.41 to 1.37)
Age 55 to 64 years (N=16 589)	0.59 (0.57 to 0.84)**	0.70 (0.58 to 0.85)**	0.79 (0.58 to 1.07)
Age 65 to 74 years (N=14 630)	0.79 (0.65 to 0.96)*	0.98 (0.83 to 1.15)	0.82 (0.62 to 1.07)
Age ≥75 years (N=26 867)	0.89 (0.79 to 1.01)	0.88 (0.79 to 0.99)*	0.90 (0.75 to 1.09)
Good prescription generosity (N=32 070)	0.91 (0.81 to 1.02)	0.81 (0.72 to 0.90)**	0.77 (0.65 to 0.93)*
Clinical subgroups			
Ischemic stroke (N=6205)	0.85 (0.70 to 1.02)	1.43 (1.17 to 1.74)**	1.25 (0.87 to 1.81)
Venous thromboembolism (N=5923)	0.50 (0.35 to 0.72)**	0.84 (0.59 to 1.21)	0.87 (0.45 to 1.69)
Congestive heart failure (N=16 265)	0.88 (0.75 to 1.03)	0.97 (0.84 to 1.11)	0.93 (0.75 to 1.15)
Acute myocardial infarction (N=2501)	0.97 (0.65 to 1.45)	1.14 (0.81 to 1.62)	0.72 (0.50 to 1.04)
Renal impairment (N=6727)	0.74 (0.57 to 0.96)*	1.52 (1.27 to 1.81)**	0.87 (0.60 to 1.24)
Diabetes (N=19 567)	0.76 (0.66 to 0.88)**	0.93 (0.82 to 1.05)	0.91 (0.73 to 1.12)
ATRIA<4 (low bleeding risk) (N=48 269)	0.89 (0.80 to 0.99)*	0.85 (0.77 to 0.94)*	0.92 (0.79 to 1.08)
ATRIA=4 (intermediate bleeding risk) (N=5659)	0.84 (0.64 to 1.09)	0.61 (0.45 to 0.82)*	0.76 (0.49 to 1.20)
ATRIA ≥5 (high bleeding risk) (N=11 007)	0.73 (0.60 to 0.90)*	1.16 (0.99 to 1.36)	0.82 (0.60 to 1.12)
CHA_2DS_2-VASc=1 (intermediate stroke risk) (N=11 004)	1.01 (0.77 to 1.31)	0.65 (0.49 to 0.87)*	0.55 (0.33 to 0.91)*
CHA_2DS_2-VASc≥2 (high stroke risk) (N=48 552)	0.84 (0.77 to 0.92)**	0.93 (0.85 to 1.01)	0.91 (0.79 to 1.04)



AF indicates atrial fibrillation; AMI, acute myocardial infarction; HR, hazard ratio; PS, Propensity score.
*P<0.05; **P<0.001.

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Disclosures

Dr Rhoney, Dr Fang, Dr Gehi, and Dr Lauffenburger have nothing relevant to declare. Dr Brookhart has received research support from Amgen for unrelated projects and has served as a scientific advisor for Amgen, Merck, and GSK (honoraria received by institution). He received consulting fees from RxAnte and World Health Information Consultants. Dr Farley has received consulting support for unrelated projects from Daiichi-Sankyo.

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